

FDA's Response to Issues Raised by the PET Community Regarding the 1999 Preliminary Draft Regulations on CGMP for PET Drugs

In its comments on the preliminary draft regulations on CGMP for PET drug products that FDA issued in September 1999, the PET community focused on five major concerns. These were: (1) requirements for not-for-profit institutions vs. commercial manufacturers, (2) identity and sample testing of PET drug components, (3) reserve samples, (4) release of product after equipment breakdown, and (5) methods validation. FDA addresses some of these issues in the preliminary draft proposed rule (PDPR) on PET drug CGMP; other issues are addressed in FDA's draft guidance on CGMP for PET drugs. Notices of the availability of the PDPR and the draft guidance were published in the *Federal Register* on April 1, 2002.

Following is a summary of FDA's response to these issues raised by the PET community:

- Relevant differences between not-for-profit institutions and commercial manufacturers:

Section 121 of the Food and Drug Administration Modernization Act directs FDA to take due account of any relevant differences between not-for-profit institutions and commercial manufacturers in developing approval procedures and CGMP for PET drugs. The PET community noted that this issue was not specifically addressed in the preliminary draft regulations.

The draft guidance notes that we closely examined the operations of many PET drug producers, including not-for-profit institutions and commercial manufacturers. We reached the conclusion that a PET center's status as a not-for-profit or for-profit entity does not have a significant bearing on the quality of drugs that it produces or the methods, facilities, and controls it needs to ensure product quality. Instead, production and CGMP differences are a function of the size, scope, and complexity of a PET center's operations. The draft guidance states that we have designed the CGMP regulations to be sufficiently flexible to accommodate not-for-profit, academically oriented institutions that make PET drug products for their own patients and research use as well as larger commercial producers that serve a greater number of patients in a broader region. For many aspects of CGMP, the draft guidance makes different recommendations depending on the size, scope, and complexity of a PET center's operations.

- Identity testing and sample testing:

The preliminary draft regulations stated that an identity test must be conducted on each lot of PET drug components, containers, and closures. They also stated that a representative sample of each lot of component, container, and closure must be tested for conformity to its written specifications. However, a report of analysis from the supplier could be accepted provided the PET center established the reliability of the supplier's test results, performed at least one specific identity test on each lot of

components, and conducted at least a visual identification of each lot of containers or closures. The PET community expressed concerns about certain aspects of these requirements.

The PDPR clarifies when identity testing must be conducted on a lot of a PET drug component. Rather than having to conduct an identity test on each lot of all components, a PET center would only have to test each lot of a component that yields an active pharmaceutical ingredient and each lot of an inactive ingredient (the PDPR would not require identity testing of reagents and solvents). If the PET center uses as an inactive ingredient a product that is marketed as a finished drug product intended for intravenous administration, the PET center would not have to perform a specific identity test on that ingredient. Regarding sample testing to ensure conformity with specifications, the PDPR deletes the requirements (when relying on a supplier's report) to also perform a specific identity test on each lot of component and conduct a visual identification of each lot of containers and closures.

- Reserve samples:

The preliminary draft regulations contained a requirement to keep a reserve sample from each batch of a PET drug product for thirty days. The PET community opposed this requirement, noting that sometimes a batch contains only one vial and a patient may require the entire batch.

The PDPR deletes the requirement to keep a reserve sample from each batch.

- Release of product after equipment breakdown:

The preliminary draft regulations stated that a PET center must conduct laboratory testing to confirm that each PET drug meets the acceptance criteria before release of the drug product. The PET community stated that it would like to be able to release a PET drug product when a PET center was unable to complete a particular analytical test due to a temporary equipment breakdown.

In the PDPR, we state that we are considering whether to include a provision that would permit final release of a PET drug product even though the PET center could not complete a required finished-product test because of equipment failure. However, because we do not want to create an exception that would expose patients to unnecessary risks for the sake of convenience, we believe that such a release would only be appropriate under certain conditions. To help determine whether the proposed exemption is appropriate, we are asking for comments on issues relating to equipment failure.

- Methods validation:

The preliminary draft regulations stated that the processing of each PET drug must be validated according to established procedures. The PET community suggested that

retrospective, repeated end-product validation is appropriate for the validation of many of the methods used in producing well-established PET drugs.

The draft guidance basically agrees. It states that for a PET center that has an established history of PET drug production, validation of a PET drug can be conducted retrospectively, provided that the current process is supported by adequate accumulated data to support a conclusion that the process is normally sufficiently capable of yielding batches meeting predetermined specifications.